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SYSTEMATIC REVIEW

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Efficacy and safety of probiotic supplements on cognitive function: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Objective This systematic review and meta-analysis aimed to evaluate the efficacy and safety of probiotic supplementation on cognitive function in individuals over 18 years of age.

Methods Randomized clinical trials (RCTs) assessing the impact of probiotics on cognitive function were included. Searches were conducted across four medical databases from inception to August 2024. The outcomes were cognitive function measured by Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Cognition Categorical Fluency Test (CFT), and adverse events. Data were extracted and analyzed using a random-effects model, with results reported as mean differences (MD) and relative risks (RR) with 95% confidence intervals (CI). To evaluate statistical heterogeneity, the I^2 statistic and the tau squared value (τ^2) were used. The risk of bias was assessed using the RoB 2.0 tool, and the certainty of evidence was evaluated with GRADE.

Results A total of 34 RCTs involving 2,390 participants were included in the meta-analysis. Limited evidence suggests a possible improvement in cognitive function from probiotics use at 12 weeks (MD 4.23, 95% CI 2.77 to 5.68; certainty of evidence (CoE) was low, $I^2 = 0\%$) for MMSE and cognitive function (MD 1.21; 95% CI 0.06 to 2.36; certainty of evidence (CoE) was low; $I^2 = 35\%$) for MoCA; however, due to the very low certainty found, the evidence is very uncertain. On the other hand, probiotic supplementation can improve cognitive performance, as measured by CFT (MD 3.94, 95% CI: 3.20 to 4.69, low certainty of evidence; $I^2 = 0\%$). Probiotics did not reduce the risk of any adverse event (RR 0.91, 95% CI 0.65 to 1.27; Certainty of evidence (CoE) was Very Low).

Conclusions Our study found that probiotics improved cognitive function, especially after 12 weeks of supplementation, using the MoCA test. However, although probiotics show potential benefits, the current evidence remains highly uncertain, warranting further rigorous trials.

Keywords Probiotics, Cognitive function, Gut-brain axis, Meta-analysis, Randomized clinical trials

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Introduction

Cognitive impairment is a prevalent condition in the general population, particularly among aging individuals with a prevalence of up to 41% and an incidence of up to 76.8 per 1000 person-years [1]. In recent decades, there has been a growing interest in understanding the relationship between gut microbiota and brain health. This has led to the emergence of the gut-brain axis as a crucial mechanism through which intestinal microorganisms may influence central nervous system function [2, 3]. Probiotics, widely recognized for their beneficial effects on digestive health, have been proposed as a potential intervention to modulate cognitive function by influencing neuroinflammation, neurotransmitter production, and gut barrier integrity [4, 5]. Given the increasing prevalence of neurodegenerative diseases, identifying non-invasive strategies to preserve cognitive health is a public health priority [6].

Numerous studies have demonstrated that the gut microbiota plays a fundamental role in brain circuitry, neurophysiological processes, and cognitive function [7]. Specifically, probiotics, which contain beneficial live microorganisms such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum*, have been investigated for their role in improving or preserving cognitive function [8]. However, while several systematic reviews have explored this potential relationship, many lack standardized methodologies to assess the certainty of evidence, limiting the robustness of their conclusions. Previous meta-analyses have focused primarily on older adults or people with Alzheimer's disease and mild cognitive impairment, and their findings remain inconsistent and did not examine the effect of probiotics on broader adult populations, such as healthy middle-aged people [9, 10]. In addition, the difference in cognitive assessment tools, probiotic strains, and study designs poses significant limitations to interpreting these findings. Furthermore, small sample sizes and inconsistencies in probiotic dosages hinder the ability to draw definitive conclusions regarding their efficacy and safety. This systematic review addresses these key gaps by including the largest number of randomized clinical trials to date (n = 34), evaluating both the efficacy and safety of probiotics, and applying robust methodological tools such as Cochrane RoB 2.0 and the GRADE system. Unlike previous meta-analyses that combined studies with various cognitive assessment tools, which differ in scoring scales, domains assessed, and sensitivity, our study conducted separate meta-analyses for each standardized test (MMSE, MoCA, and CFT) and probiotic characteristics (strains and population type), which allowed us to reduce heterogeneity and improve the comparability of results. Our findings offer a more up-to-date, rigorous, and reliable synthesis of the evidence on the use of probiotics on cognitive function in adults. We also recognize that the small sample sizes of many previous studies and the inconsistency in the doses administered make it difficult to draw definitive conclusions about their efficacy and safety. In addition, the impact of probiotics may differ significantly between adults and other populations such as children or older adults with severe impairment. Therefore, this review focuses specifically on adults, a group facing an increasing risk of mild cognitive impairment and neurodegenerative diseases [11], and in whom early intervention with probiotics may have a clearer preventive or therapeutic role. These limitations and gaps in literature underscore the need for an updated, methodologically rigorous systematic review and meta-analysis that standardizes inclusion criteria and conducts subgroup analyses to more accurately assess both the efficacy and potential risk of probiotics use in this population.

This systematic review and meta-analysis aim to synthesize the available evidence on the effects of probiotic supplementation on cognitive function in adults, assessing both benefits and potential adverse effects. By employing rigorous methodological approaches, including the GRADE system for evidence certainty and standardized criteria for inclusion, this study seeks to provide a comprehensive and reliable assessment of the clinical utility of probiotics in cognitive enhancement.

Methods

This study was a systematic review and meta-analysis conducted following PRISMA 2020 guidelines (Supplemental Table 1). The protocol was registered in PROSPERO (code: CRD42025641154).

Search strategy

A comprehensive search was performed in PubMed, Scopus, Web of Science, and EMBASE from inception until August 2024. The search strategy incorporated key phrases, MeSH terms (PubMed), and Emtree thesauri (Scopus, EMBASE), with "Cognitive Function" AND "Probiotics" as the primary search terms (Supplementary Table 2). No language or publication date restrictions were applied. Additionally, reference lists of relevant studies and review articles were manually searched. Due to the high volume of studies retrieved, gray literature was not included.

Eligibility criteria

This study included Phase 2 or 3 randomized controlled trials (RCTs) involving participants aged 18 years or older, with cognitive impairment or at risk of cognitive decline, including those with Alzheimer's disease or mild cognitive impairment. Eligible trials compared probiotic supplementation in various formulations (capsules,

sachets, liquids) against placebo or active control. Probiotic strains predominantly included *Lactobacillus* and *Bifidobacterium* species, administered either alone or in combination. Exclusion criteria included conference abstracts, systematic and narrative reviews, case reports, case series, letters to the editor, and clinical trials involving infants, adolescents, or animals.

Outcomes

The primary outcome was cognitive function, assessed using the Mini-Mental State Examination (MMSE) at 8 and 12 weeks, the Montreal Cognitive Assessment (MoCA-J) at 12 weeks, and the Categorical Fluency Test (CFT) at 12 weeks. We decided to use these tools because they are the most common tools for detecting cognitive impairment in multiple studies [12–15]. Results were reported as means, standard deviations, or mean differences. Secondary outcomes included the incidence of adverse effects, measured as frequencies and relative risk. Quality of life outcome was also originally considered as secondary outcome, but none of the included trials assessed it. The MMSE is a widely used cognitive screening tool assessing temporal and spatial orientation, memory, attention, language, and the ability to follow simple instructions. The MoCA is a more sensitive screening tool for detecting mild cognitive impairment, covering areas such as attention, memory, language, visuospatial skills, executive functions, and orientation.

Data extraction

Following previous methodologies [16, 17], search results were compiled into a single library, and duplicates were removed. Four reviewers (NCG, IMC, LChF, DAG) independently screened studies in two phases: [1] title and abstract screening using predefined inclusion and exclusion criteria via the Rayyan platform, and [2] full-text review of eligible studies with justifications for inclusion/exclusion. Data extraction was performed in duplicate using a structured Excel spreadsheet, capturing study details, intervention and control descriptions, and outcome measures. Discrepancies were resolved through discussion with a senior reviewer (JJB).

Risk of bias assessment

Pairs of reviewers (CQV, IMC, PTB, ABP) independently assessed the risk of bias for each included RCT using the Cochrane Risk of Bias Tool 2 (RoB 2) [18]. Disagreements were resolved by discussion with a senior reviewer (JJB). Studies were categorized as having a low, some concerns, or high risk of bias.

Data synthesis

A random-effects model with the inverse variance method was used for meta-analyses. The Paule-Mandel method estimated between-study variance (tau^2) [19]. Relative risks (RR) with 95% confidence intervals (CI) were reported for dichotomous outcomes, and the Hartung-Knapp method was applied for meta-analyses involving more than five studies [20]. Statistical heterogeneity was assessed using the I^2 statistic, categorized as low (< 30%), moderate (30–60%), or high (>60%). Sensitivity analyses were conducted using fixed-effects models and the Mantel-Haenszel method. Analyses were performed using the metabin function in R 3.5.1 (www.r-project.org).

For crossover trials, data were extracted exclusively from the first treatment period to minimize carryover effects. If adequate washout periods and intra-subject variability adjustments were reported, paired mean differences were used; otherwise, trials were analyzed as parallel-group studies following Cochrane Handbook recommendations.

Subgroup analyses were planned a priori to explore potential sources of heterogeneity. Two subgroup comparisons were conducted: by probiotic formulation (single - strain vs. multi-strain) and by population type (healthy adults, people with mild cognitive impairment, and patients with Alzheimer's disease).

GRADE assessment

The certainty of evidence for all reported outcomes was assessed by consensus (JJB, NCG, CQV, HTCh) using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach [21]. Factors considered included risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence was categorized as high, moderate, low, or very low, and results were summarized in Summary of Findings (SoF) tables using GRADEpro GDT (Supplemental Table 3).

Given the heterogeneity of the included studies, probiotic strains and doses were systematically standardized for comparability. Strains were classified by genus and species (*Lactobacillus*, *Bifidobacterium*, and others), with subgroup analyses distinguishing strains based on functional mechanisms (e.g., modulation of neuroinflammation, neurotransmitter production, gut barrier integrity).

Doses were converted to Colony Forming Units (CFU) per day for consistency across studies. Various dosage formats (sachets, capsules, liquids) were normalized using standardized conversion methods. Dose categories (low, medium, high) were established, and nonlinear regression models with restricted cubic splines were implemented to assess potential dose-response relationships.

To further mitigate heterogeneity and improve robustness, sensitivity analyses were conducted, excluding

studies with extreme dosage variations or unspecified probiotic strain combinations.

Results

Selection of studies

We evaluated 2182 studies in the different databases, of which 680 were duplicates and were removed. Of the remaining 1,502, 1,453 were excluded by title and abstract (because they did not report a population or outcome based on different eligibility criteria). Finally, 34 studies were included in the systematic review [22–55] (Fig. 1).

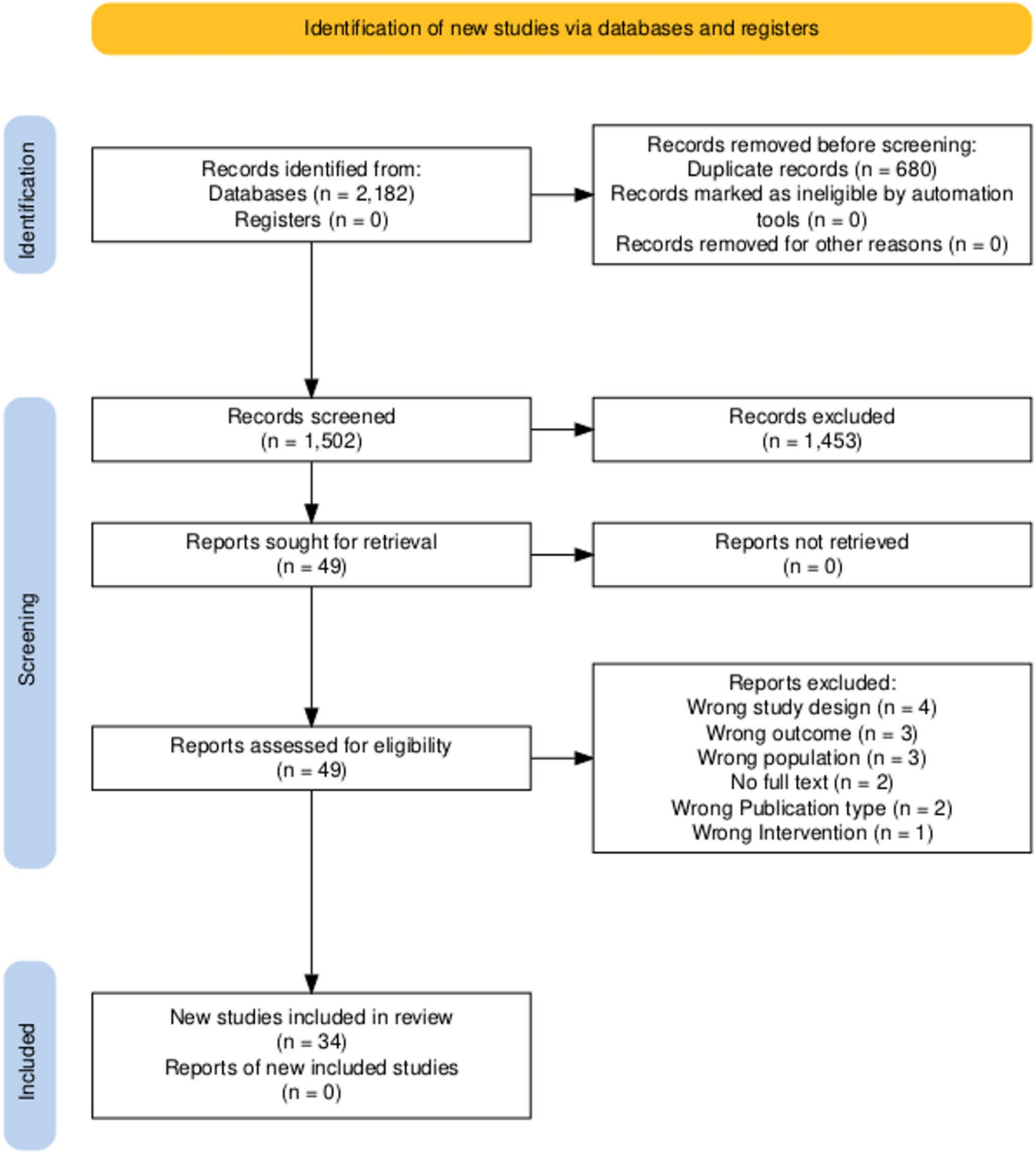

Fig. 1 PRISMA 2020 flowchart for selection of studies

Characteristics of included studies

The studies in this systematic review share several common characteristics in design, population, and intervention. All the trials were randomized clinical trials that aimed to assess the efficacy and safety of probiotic supplementation on cognitive function. Most of the studies involved participants who were middle-aged or older adults, with the average age across the trials being approximately 53 years. The number of participants enrolled in each trial varied, but on average, the sample size was around 70 individuals per study. Gender distribution showed that, on average, 40.6% of the participants were male, indicating a balanced representation of both genders in most trials (Table 1). Regarding the intervention, probiotic supplementation was administered in different forms, including capsules, sachets, or liquids, depending on the specific study. The duration of these interventions generally ranged from 12 to 24 weeks, with most studies implementing daily or twice-daily dosing regimens. All studies included a placebo group for comparison, that while they may ensure rigorous control of potential biases, they may still have methodological limitations. Additionally, the studies reported no significant adverse events related to the probiotic treatments (clinically verified), supporting the overall safety profile of the interventions; however, given the very low certainty, this should be interpreted with caution. These commonalities across the studies provide a robust foundation for comparing the outcomes and drawing conclusions regarding the impact of probiotics on cognitive function (Table 2). The excluded studies and their justification are listed in Supplementary Table 4.

The studies included in this systematic review analyzed both single-strain and multi-strain probiotic formulations. The most investigated were *Lactobacillus* and *Bifidobacterium*. Among the single-strain probiotics, *Lactobacillus plantarum* and *Bifidobacterium breve* were the most frequently studied, particularly in populations with mild cognitive impairment or major depression. The most frequently used multi-strain formulations included *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Lactobacillus plantarum*.

These multi-strain interventions were predominantly studied in individuals with Alzheimer's disease, mild cognitive impairment, and other cognitive conditions. In Alzheimer's disease, combinations of *Lactobacillus* and *Bifidobacterium* were the most frequently evaluated, whereas in schizophrenia, up to six-strain combinations from these genera were used Risk of Bias Assessment.

The risk of bias was evaluated across 34 studies using the RoB 2 tool. The assessment revealed that 37% of the studies (n = 13) [25, 26, 29, 30, 38, 39, 42, 43, 46–48, 51, 55] had a low overall risk of bias, 34% (n = 12) [27, 31, 32, 34, 36, 40, 44, 45, 49, 52–54] exhibited some concerns, and 29% (n = 9) [22–24, 28, 33, 35, 37, 41, 50] were classified as having a high risk of bias. In most studies, the majority of RoB 2 domains were rated as low risk. However, specific concerns were identified in key areas. The randomization process and participant recruitment presented an unclear risk of bias in 12 out of 34 studies. Deviations from intended interventions were observed in eight studies, leading to a high risk of bias. Missing outcome data were a concern in two studies, while measurement of outcomes was unclear in four studies. Selective outcome reporting was identified as unclear in seven studies (Fig. 2).

Summary of results and certainty of evidence

The evidence regarding probiotic supplementation for cognitive function varied depending on the follow-up duration and the assessment tool used.

The Mini-Mental State Examination (MMSE) was used to evaluate cognitive function at 8 and 12 weeks. At the 8-week follow-up which included two RCTs [28, 41], the effect of probiotics compared to placebo was highly uncertain, with a mean difference of −0.02 points (95% CI: −0.69 to 0.65) across two RCTs involving 146 participants. The certainty of the evidence was rated as low (Fig. 3). At 12 weeks, two RCTs [40, 49] involving 160 participants showed a potential increase in cognitive function in the probiotic group, with a mean difference of 4.23 points (95% CI: 2.77 to 5.68), though the certainty of evidence remained low (Fig. 4).

The Montreal Cognitive Assessment (MoCA) was evaluated at 12 weeks. The results from three RCTs [26, 49, 54] with 148 participants suggested that probiotics might improve cognitive function compared to placebo, with a mean difference of 1.21 points (95% CI: 0.06 to 2.36). However, the certainty of the evidence was rated as low (Fig. 5).

The Categorical Fluency Test (CFT) was assessed at 12 weeks. Data from one RCTs [40] with 120 participants indicated that probiotic supplementation may improve cognitive performance, with a mean difference of 3.94 points (95% CI: 3.20 to 4.69). The certainty of the evidence was rated as low (Fig. 6).

Subgroup analysis showed that single-strain probiotics data from one RCTs [40], may improve cognitive function, with a mean difference of 4.67 points (95% CI: 1.13 to −8.22), although the evidence was of low certainty. In contrast, multi-strain formulation data from four RCTs [26, 36, 49, 54] did not show a significant effect (MD: 1.76; 95% CI: −0.96 to 4.49), and the certainty of the evidence was very low (Supplemental Fig. 1).

In a subgroup analysis by population type, data from one RCT [40] on people with Alzheimer's disease, probiotics may improve cognitive function (MD: 4.67; 95% CI:

Table 1 Characteristics of included studies

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Agahi A.	2018	Iran	Randomized, double-blind, placebo-controlled clinical trial	June 2017 to August 2017	Supported by Grant No. 96,042 from the Deputy of Research of Kashan University of Medical Sciences (KAUMS)	Patients with Alzheimer's Disease (AD) aged 65–90 years residing in various welfare organizations in Iran	Based on NINDS-ADRDA criteria and revised criteria from the National Institute on Aging-Alzheimer's Association	65–90 years old	AD patients diagnosed based on specific criteria and confirmed with Test Your Memory (TYM) cognitive test	Patients with metabolic disorders, chronic infections, or other clinically relevant disorders	48	Control group: 43.5%, Probiotic group: 28%
Akhgarjand C.	2022	Iran	Randomized, double-blind, placebo-controlled clinical trial	October 2021 to March 2022	Supported by a grant from Tehran University of Medical Sciences	Subjects with mild and moderate Alzheimer's Disease (AD), aged 50–90 years	NINDS-ADRDA criteria and National Institute on Aging Alzheimer's Association guidelines	50–90 years old	Aged 50–90 years, ability to tolerate oral medication, mild or moderate AD	Allergy to probiotic supplements, reluctance to continue cooperation, drastic changes in diet, inflammatory diseases, etc.	90	33.3% (16 males in each group)
Asaoka D.	2022	Japan	Randomized, double-blind, placebo-controlled clinical trial	March 2018 to June 2020	Supported by Juntendo University and Morinaga Milk Industry Co., Ltd.	Older adults aged 65–88 years with suspected mild cognitive impairment (MCI)	Clinical criteria of MCI (DSM-5) with MMSE scores between 22 and 26 and Clinical Dementia Rating (CDR) = 0.5	65–88 years old (Mean: Probiotic group 77.2 years, Placebo group 78.9 years)	Aged 65–89 years, suspected MCI, memory complaints, MMSE scores between 22 and 26, and CDR = 0.5	Severe diseases (e.g., cerebrovascular, heart, liver), major psychiatric disorders, substance abuse, cognitive impairment due to vitamin deficiencies, participation in other drug studies	115	Probiotic group: 47.3%, Placebo group: 41.7%
Ascone L.	2022	Germany	Double-blind, randomized-controlled trial (RCT)	January 2018 to November 2019	No specific grant from any funding agency, commercial or not-for-profit sectors	Healthy individuals aged 18–40 years, right-handed	N/A (study focused on healthy individuals)	18–40 years (Median: Probiotic group 24.5 years, Placebo group 27.0 years)	Age 18–40 years, right-handed	Neurological, mental, chronic, or severe somatic disorders, veganism/vegetarianism, recent antibiotic intake, conscious probiotic diet/intake, lactose intolerance, concurrent participation in a drug trial	59	Probiotic group: 43%, Placebo group: 45%

Table 1 (continued)

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Azuma N.	2023	Japan	Randomized, double-blind, placebo-controlled trial	Not specified	Supported by Ezaki Glico Co., Ltd.	Japanese men and women between 50 and 80 years of age with mild cognitive decline due to aging	MMSE-J score of 24 or higher, MoCa-J score of 17 or higher, GDS-S-J score of 5 or less	50–80 years old	Mild cognitive decline, subjective memory loss, ability to consent	Mental disorders, serious diseases, smokers, heavy alcohol users, recent antibiotic use, etc.	80	Not specified explicitly for each group
Bartos A.	2023	Czech Republic	Double-blind, randomized, placebo-controlled clinical trial with cross-over design	January 2021 to April 2022	Supported by the Ministry of Industry and Trade (Trio program FV40032) and the Ministry of Health, Czech Republic	Community-dwelling older adults aged 55–80 years with normal or mildly impaired cognition	Normal cognition or mild cognitive impairment; no specific medical diagnosis provided beyond cognitive status	55–80 years old (Mean age: 69 years for Probiotic-first group, 71.5 years for Placebo-first group)	Aged 55–80 years, Czech as a native language, preserved activities of daily living, good sight and hearing	Diseases of the digestive tract, neurological brain diseases, psychiatric diseases or treatment, oncological diseases, recent use of cognitive enhancers or probiotics within 3 months	91	37% in the Probiotic-first group, 44% in the Placebo-first group
Benton D.	2007	UK (Wales)	Double-blind, placebo-controlled trial with random allocation	Not specified	Funded by Yakult, Japan	132 healthy members of the general population, mean age 61.8 years	Self-reported good health, no diagnosis of depression, dementia, schizophrenia, or significant heart, lung, kidney, or liver issues	Mean age: 61.8 years (Range: 48–79 years)	Healthy individuals who did not consume yogurt containing live bacteria	Depression, dementia, schizophrenia, neurological disorders, significant heart, lung, kidney, or liver conditions, recent malignancy, unstable diabetes or hypothyroidism, uncontrolled hypertension	132	39% male (51 males, 75 females)
Chung Y.	2014	Korea	Double-blind, randomized controlled trial	Not specified	Sponsored by ILDONG Pharmaceutical Co., Ltd.	47 healthy older adults, aged 60–75 years	MMSE-K score ≥ 24	60–75 years	Experience using computers, education above middle school, within ± 30% of ideal body weight, understanding of the study objectives	Axis I mental disorders, alcohol abuse or dependence, gastrointestinal disease, significant neurological or medical illnesses, use of supplements or herbal medicines during the 4 weeks preceding the study, compliance less than 70%	47	55.6% male, 44.4% female

Table 1 (continued)

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Czajeczny D.	2021	Poland	Randomized, single-blind, placebo-controlled trial	October 2018 - July 2019	Supported by Poznan University of Medical Sciences grant for young scientists	53 healthy young adult women, with 38 completing the trial	General health information obtained during initial interviews	19–31 years (mean age: 23.47 ± 4.19 for supplementation group, 23.06 ± 3.11 for placebo group)	Female, experience using computers, education above middle school, within ± 30% of ideal body weight, understanding of study objectives	Gastroenteric, endocrine, neurological, or psychiatric disorders, antibiotic treatment up to 3 months prior to supplementation, current probiotic supplementation	53	Not applicable (study only included females)
Fei Y.	2023	China	Randomized, placebo-controlled trial	December 2021 - December 2022	Supported by Sichuan Provincial Science and Technology Department, Sichuan Traditional Chinese Medicine Administration, etc.	42 older adults with mild cognitive impairment (MCI), 40 completed the study	Petersen diagnostic criteria of MCI	Average age: 76.40 years (probiotics group), 75.30 years (placebo group)	Aged over 60 years, meeting Petersen diagnostic criteria for MCI, no serious organ dysfunction, no chronic disease exacerbation, no visual/hearing impairment	Participation in other clinical studies, allergies to dairy products	42	Probiotics group: 10 males, Placebo group: 11 males
Hsu Y.	2023	Taiwan	Randomized, double-blind, active-controlled trial	2020 to 2022	Supported by a grant from Glac Biotech Co., Ltd., Tainan, Taiwan	40 participants with Alzheimer's dementia, all undergoing standard treatment with acetylcholinesterase inhibitors or memantine	Based on DSM-V, NINCDS-ADRDA, or NI-AAA (2011) guidelines for Alzheimer's disease	50 to 90 years (mean age: treatment group 75.4 ± 8.0 years; control group 75.8 ± 7.3 years)	Clinically diagnosed Alzheimer's dementia, aged 50–90, with MMSE scores between 10 and 25, and CDR scores of 0.5, 1, or 2	Dementia other than Alzheimer's disease, vitamin B12 deficiency, thyroid function abnormalities, severe organ dysfunction, severe brain trauma, psychiatric disorders, etc.	40	Control group: 8 males, Treatment group: 4 males
Yun-Ha Hwang	2019	South Korea	Randomized, double-blind, placebo-controlled clinical trial	Not specified	Supported by the Korea Health Industry Development Institute (KHIDI)	100 participants with mild cognitive impairment	Mild cognitive impairment (MCI)	69.2 years in placebo group, 68.0 years in DW2009 group	Not specified	Not specified	100 (50 intervention, 50 placebo)	Not specified
Inoue T.	2018	Japan	Randomized, double-blind, placebo-controlled trial	Not specified	Not explicitly stated	Elderly subjects	Not specified	Mean age 70.3 years (± 3.1)	Not specified	Not specified	38 participants (Probiotic group: 20, Placebo group: 18)	Probiotic group: 35%, Placebo group: 38.9%

Table 1 (continued)

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Juan	2022	China	Randomised, double-blind, placebo-controlled trial	1 st May 2018 to 8th October 2019	National Natural Science Foundation of China	Patients with breast cancer (Stage I-III)	AJCC 8th edition Stage I-III	45.31 (SD 8.48)	Newly diagnosed breast cancer, age 20–60 years, without immune diseases	History of brain injury, cerebral haemorrhage, stroke, etc.	162	Not specified
Jung P	2019	Korea	Randomized, double-blind, placebo-controlled study	Not specified	National Research Foundation of Korea	69 participants, aged 18–65	None (Healthy adults)	31.83 ± 16.32 years (Placebo), 32.86 ± 17.61 years (FSJ)	Healthy adults, aged 18–65	Not specified	69 participants (Placebo: 36, FSJ: 33)	Not specified
Kelly J	2017	Ireland	Randomized, placebo-controlled, cross-over design	Not specified	Science Foundation Ireland (SFI)	29 healthy male volunteers	None (Healthy males)	20–33 years	Male participants aged between 18–40 years, able to speak English, in good health	Significant acute or chronic illness, interference with study objectives	29	100%
Kikuchi-Hayakawa H	2023	Japan	Double-blind, randomized, crossover, placebo-controlled trial	August to December 2021	Yakult Central Institute	12 healthy office workers	Sleep complaints	40–59 years	Healthy office workers with sleep complaints	History of sleep-related illnesses, smoking, use of medications influencing sleep	12	5 males, 7 females
Kim CS	2021	Republic of Korea	Randomized, double-blind, placebo-controlled, multicenter trial	March 2018 to March 2019	National Research Foundation of Korea	63 healthy older adults (≥ 65 years)	None (Healthy older adults)	72.00 years (Placebo), 71.11 years (Probiotics)	Healthy adults aged 65 or older, capable of independent living	Use of antibiotics, anti-inflammatory medications, or gastrointestinal medicine in the past 3 months	63 (Placebo: 31, Probiotics: 32)	Not specified
Kobayashi Y	2019	Japan	Randomized, double-blind, placebo-controlled trial	Not specified	Wageningen Academic Publishers	121 elderly subjects with memory complaints	Mild cognitive impairment	50–80 years	Age 50–80 years, MMSE score 22–27	Diagnosed with dementia, history of psychiatric disorders, major surgeries, or serious illnesses	121 (B. breve A1: 61, Placebo: 60)	50% male
Lee C	2018	Malaysia	Randomized, double-blind, placebo-controlled study	Not specified	School of Industrial Technology, Universiti Sains Malaysia	103 stressed adults	PSS-10 questionnaire	31.7 ± 11.1 years	Adults aged 18–60 years, moderate stress levels	Severe illness, long-term medication, HIV/AIDS, etc.	103 (P8: 52, Placebo: 51)	Not specified

Table 1 (continued)

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Mohammadi A.	2024	Iran	Double-blinded, randomized controlled trial	December 2021 to April 2022	No funding source	70 schizophrenic patients aged 18–65 years	DSM-5 for Schizophrenia	Intervention group: 50.29 ± 9.61 years; Placebo group: 52.02 ± 8.32 years	Age 18–65 years, capacity for signing informed consent, at least fifth-grade education, stable on psychotropics for at least 6 months	History of brain injury, head trauma, mental retardation, Parkinson's disease, substance use, allergy to probiotics, recent antibiotics use, pregnancy, significant medical disorders, exposure to weight-loss medicines	70 (Probiotic: 35, Placebo: 35)	Probiotic group: 73.5%, Placebo group: 71.4%
Ohsawa K.	2018	Japan	Randomised, double-blind, placebo-controlled trial	September 2013 to March 2014	Asahi Group Holdings, Ltd.	61 healthy Japanese men and women aged 50–70 years	Self-identified forgetfulness or forgetfulness identified by a close relative	Mean age 57.8 ± 5.9 years (Placebo), 58.5 ± 6.5 years (Test group)	Healthy middle-aged adults with forgetfulness, baseline RBANS score of 29–52	Milk or soybean allergy, history of stroke, severe illness, excessive smoking, alcohol use, dietary supplement use, etc.	61 (Placebo: 30, Test: 31)	Not specified
Önning G.	2023	Ireland	Randomized, double-blind, placebo-controlled, parallel-designed study	June 2021 to March 2022	Probi AB, Lund, Sweden	129 moderately stressed subjects (aged 21–52 years)	Perceived Stress Scale (PSS) and Hospital Anxiety and Depression Scale (HADS)	Mean age: 35.2 years	PSS score between ≥ 14 and ≤ 26, HADS score of ≤ 10	Active IBS, chronic intestinal disease, psychiatric illness, use of psychotropics, or prohibited medication	129 (LPHEAL9: 65, Placebo: 64)	LPHEAL9: 65% female, Placebo: 67% female
Papalini S.	2018	The Netherlands	Randomized, double-blind, placebo-controlled, between-subjects intervention study	Not mentioned	Dutch Ministry of Economic Affairs, Winclove Probiotics B.V., and other grants	Healthy female volunteers, aged 18–40, right-handed, using hormonal contraceptives, BMI 18–25	No specific disease criteria, healthy participants	Mean age: 21–22 years	Female, 18–40 years, right-handed, BMI 18–25, using hormonal contraceptives	History of psychiatric, neurological, gastrointestinal, endocrine disorders, medication use, probiotic/prebiotic supplementation, smoking, recent antibiotic use, lactose intolerance, vegan diet, high alcohol intake	58	0

Table 1 (continued)

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Roman P.	2019	Spain	Randomized, double-blind, placebo controlled.	February 2013 to March 2016	Carlos Health Institute III (Madrid, Spain) Mendes S.A. (Lugano, Switzerland) and Actial pharmaceutical LDA (Funchal, Portugal).	Patients with cirrhosis	Cirrhosis was diagnosed by means of clinical, analytical, and ultrasonographic findings or by liver biopsy.	Mean age 65.8 years (Probiotic), 64.0 years (Placebo)	Patients with cirrhosis who experienced cognitive dysfunction and/or falls during the previous year. Cognitive dysfunction with psychometric hepatic encephalopathy score (PHES) less than −4	Hospitalization during the previous month, hepatocellular carcinoma or any other neoplasm, manifest acute or chronic hepatic encephalopathy, neurological disease, active alcohol consumption (in the previous 3 months), clinically significant cognitive impairment, inability to perform psychometric tests, severe comorbidities, life expectancy less than 6 months, any treatment with non-absorbable disaccharides, laxatives, antibiotics and/or antivirals in the previous 3 months and refusal to participate in the study.	18 (Probiotic) 18 (Placebo)	Probiotic: 33.3%, Placebo: 44.4%
Roman P.	2018	Spain	Randomized controlled trial	December 2015 to February 2016	Spanish Ministry of Economy and Competitiveness, ERDF funds, University of Almeria	Patients with fibromyalgia	Fibromyalgia according to the American College of Rheumatology	Mean age 55.00 years (Probiotic), 50.27 years (Placebo)	Fibromyalgia diagnosis, no severe intestinal disease, no psychiatric disorders	Using antibiotics, pregnant, severe intestinal disease	16 (Probiotic), 15 (Placebo)	Probiotic: 6.25%, Placebo: 13.33%
Rudzki L.	2018	Poland	Double-blind, randomized, placebo-controlled trial	June 2014 to March 2016	Medical University of Bialystok, Poland	Patients with Major Depressive Disorder (MDD)	Major Depressive Disorder according to DSM-IV-R	Mean age 38.90 years (Placebo), 39.13 years (Probiotic)	MDD diagnosis, SSRI treatment, no inflammatory, autoimmune disorders	Inflammatory, oncological, autoimmune disorders, psychiatric diseases other than depression, substance abuse, smoking, BMI < 18.5 or > 30	60 (30 Probiotic, 30 Placebo)	33.3% (Placebo), 23.3% (Probiotic)
Ruiz-Gonzalez C.	2024	Spain	Double-blind, randomized, placebo-controlled crossover trial	July 2020 to April 2022	Health Research Center CEINSA and University of Almería	Healthy older adults aged 55 years or older	No severe mental illness, MMSE score above 10	Mean age 66.22 years	Age 55 years or older, voluntary participation	Severe mental illness, MMSE score below 10, medications affecting cognition	33 (27 completed the study)	30% male

Table 1 (continued)

First Author	Year	Country	Study Design	Recruitment Dates	Funding	Studied Population	Diagnostic Criteria	Age Range	Inclusion Criteria	Exclusion Criteria	Number of Participants	Male Frequency (%)
Sakurai K.	2022	Japan	Randomized, double-blind, placebo-controlled trial	October 2020 to March 2021	Meiji Co., Ltd. and University of Tokyo	Older adults aged 65 and above with declining memory	Early memory deterioration identified via MCI Screen with MPI score < 60	Mean age 76.8 years (Active), 76.9 years (Placebo)	Age 65 and above, early memory decline, no serious systemic illnesses	Diagnosed dementia, allergies to dairy products	81 participants, 78 completed (39 Active, 39 Placebo)	46% male (both groups)
Sanborn V.	2020	USA	Double-blind, placebo-controlled, randomized clinical trial	May 2017 to September 2019	i-Health, Inc., a division of Royal DSM	Healthy middle-aged and older adults aged 52–75	Cognitive function assessed via NIH Toolbox Cognition Battery	Mean age 64.3 years (SD = 5.52)	Age 52–75, no developmental, neurological, or severe psychiatric disorder	Recent use of antibiotics, prebiotics, or probiotics, severe heart, liver, kidney issues, immunosuppression	145 (Probiotic = 77, Placebo = 68)	Approximately 40% male
Schneider E.	2023	Switzerland	Randomized, double-blind, placebo-controlled trial	March 2017 to January 2020	Gertrud Thalmann-Fonds, Seerave Foundation, Kämpf-Bötschi Stiftung, Research Fund Junior Researchers of the University of Basel	Patients with Major Depressive Disorder (MDD)	ICD-10 codes F31.3-F34 for depressive episodes, HAM-D score > 7	Mean age 38.56 years (SD: 10.71)	Primary diagnosis of MDD, HAM-D score > 7, ongoing treatment for depression, no psychiatric comorbidities	Psychiatric comorbidities (e.g., schizophrenia, bipolar disorder, substance use disorder)	43 (19 Probiotic, 24 Placebo)	26% (Probiotic), 50% (Placebo)
Shi S.	2023	China	Randomized, double-blind, placebo-controlled trial	Not explicitly mentioned	National Key R&D Program of China (grant number 2021YFD1600204)	Healthy older adults aged 60–75 years	MoCA score indicative of healthy cognitive function	Mean age 64.10 years (Probiotic), 64.50 years (Placebo)	Age 60–75 years, healthy cognitive function as judged by MoCA	Obvious cognitive decline, Alzheimer's disease, major medical issues, recent antibiotic or probiotic use	60 participants (50 completed)	40% (Probiotic), 43% (Placebo)
Tamtaji O.	2019	Iran	Randomized, double-blind, controlled trial	December 2017 to July 2018	Kashan University of Medical Sciences	Patients with Alzheimer's Disease (AD)	NINDS-ADRDA criteria, revised criteria from the National Institute on Aging-Alzheimer's Association	55 to 100 years, no exact mean age provided	Age 55–100 years, diagnosed with Alzheimer's Disease	Metabolic syndrome, diabetes, cardiovascular disease, chronic infections, prior probiotic/synbiotic/antioxidant supplement intake	79 (Probiotic + Selenium = 27, Selenium = 26, Placebo = 26)	Not explicitly mentioned
Xiao J.	2020	Japan	Randomized, double-blind, placebo-controlled trial	June to August 2019	Morinaga Milk Industry Co., Ltd.	Older adults aged 50–79 years with suspected MCI	MCI diagnosis, MMSE score of 22 or more	61.1 years (SD: 7.2)	Age 50–79 years, MMSE score of 22 or more	Diagnosed with dementia, undergoing exercise or diet therapy, significant medical history	80 participants (40 Probiotic, 40 Placebo)	Probiotic: 47.5%, Placebo: 50%

Table 2 Characteristics of interventions and control

First Author	Year	Intervention Content	Duration of Intervention	Frequency of Intervention	Co-Intervention Content	Control Type	Placebo	Control Active	Adverse Event Measure
Agahi A.	2018	Probiotic supplementation with capsules containing mixtures of Lactobacillus and Bifidobacterium species	**12 weeks**	Daily	No nutritional supplements or changes in physical activity during the trial	Placebo-controlled	Capsules containing 500 mg maltodextrin	Not applicable	No significant adverse events reported
Akhgarjand C.	2022	Probiotic supplementation with either Lactobacillus rhamnosus HA-114 or Bifidobacterium longum R0175 (each containing 10^15 CFU)	12 weeks	Twice daily	None reported	Placebo-controlled	Capsules containing xylitol, maltodextrin, and malic acid	Not applicable	No serious adverse events reported
Asaoka D.	2022	Daily sachet containing lyophilized Bifidobacterium breve MCC1274 (2×10^10 CFU)	24 weeks	Once daily	None reported	Placebo-controlled	Sachets containing maize starch (identical in appearance and weight to probiotic sachets)	Not applicable	No serious adverse events reported
Ascone L.	2022	Daily dose of multi-strain probiotic (Vivomixx®), 4.4 g containing 450×10^9 CFU of various bacterial strains	4 weeks	Daily	Participants instructed not to change their diet during the intervention	Placebo-controlled	Commercially available baby milk powder (Bebivita® Anfangsmilch)	Not applicable	No significant adverse events reported
Azuma N.	2023	Dairy drink containing Bifidobacterium animalis subsp. lactis GCL2505 (1×10^10 CFU/100 g) and inulin (2.0 g/100 g)	12 weeks	Once daily	None reported	Placebo-controlled	Dairy drink without active ingredients, matched for taste and appearance	Not applicable	No significant adverse events reported
Bartos A.	2023	Daily dose of probiotics containing Streptococcus thermophilus GH, Streptococcus salivarius GH NEXARS, Lactobacilus plantarum GH, Pediococcus pentosaceus GH (106 CFU) combined with prebiotics	3 months (followed by crossover to placebo for an additional 3 months)	Once daily	None reported	Placebo-controlled	Tablets composed of semi-coarse wheat flour, starch, maltodextrin, and magnesium stearate	Not applicable	No significant adverse events reported
Benton D.	2007	Probiotic milk drink containing Lactobacillus casei Shirota (6.5×10^9 CFU)	3 weeks	Daily	None reported	Placebo-controlled	Milk-based placebo without live bacteria	Not applicable	No significant adverse events reported

Table 2 (continued)

First Author	Year	Intervention Content	Duration of Intervention	Frequency of Intervention	Co-Intervention Content	Control Type	Placebo	Control Active	Adverse Event Measure
Chung Y.	2014	Fermented milk containing Lactobacillus helveticus IDCC3801 (500, 1000, or 2000 mg)	12 weeks	Once daily	None reported	Placebo-controlled	Tablets without Lactobacillus helveticus, identical in appearance to active tablets	Not applicable	No significant adverse events reported
Czajeczny D.	2021	Daily supplementation with Bifidobacterium lactis BS01 (2×10^9 CFU) and Lactobacillus acidophilus LA02 (2×10^9 CFU)	6 weeks	Once daily	None reported	Placebo-controlled	Capsules filled with maltodextrin, identical in appearance to active capsules	Not applicable	No significant adverse events reported
Fei Y.	2023	Daily supplementation of 2 g probiotics containing a mixture of strains, including Lactobacillus plantarum, Lactococcus lactis, etc.	12 weeks	Once daily	None reported	Placebo-controlled	2 g starch capsules, identical in appearance to probiotics	Not applicable	No significant adverse events reported
Hsu Y.	2023	Probiotic capsules containing five strains (1×10^10 CFU/capsule)	12 weeks	Once daily	None reported	Active control	Not applicable (received probiotics with a lower dose of 5×10^7 CFU/capsule)	Lower dose of probiotics compared to treatment group	No significant adverse events reported
Yun-Ha Hwang	2019	DW2009 (mixture of fermented soybean with Lactobacillus plantarum C29)	12 weeks	Two capsules per day	Abstain from other nutritional supplements	Placebo	Cellulose capsules	Not applicable	Not specified
Inoue T.	2018	Sachet containing lyophilized powder of Bifidobacterium strains	12 weeks	Daily	12-week resistance-training program	Placebo	Sachet containing dextrin	Not specified	0
Juan	2022	Probiotics (three capsules, twice/day) during chemotherapy	Throughout chemotherapy	Twice/day	None specified	Placebo	Yes	None	Not specified
Jung P	2019	Lactobacillus fermented Saccharina japonica extract (FSJ)	4 weeks	Once a day	None specified	Placebo	Yes	None	Not specified
Kelly J	2017	Lactobacillus rhamnosus (JB-1)	8 weeks	Once a day	None specified	Placebo	Yes	None	Not specified
Kikuchi-Hayakawa H	2023	Lacticaseibacillus paracasei strain Shirota (LcS) in fermented milk	4 weeks	Daily	None specified	Placebo	Yes	None	Wilcoxon rank sum test
Kim CS	2021	Probiotics containing Bifidobacterium bifidum BGN4 and Bifidobacterium longum BORI	12 weeks	Twice a day	None specified	Placebo	Yes	None	Not specified

Table 2 (continued)

First Author	Year	Intervention Content	Duration of Intervention	Frequency of Intervention	Co-Intervention Content	Control Type	Placebo	Control Active	Adverse Event Measure
Kobayashi Y	2019	Bifidobacterium breve A1 capsules	12 weeks	Twice daily	None specified	Placebo	Yes	None	Wilcoxon rank sum test
Lee C	2018	Lactobacillus plantarum P8 (10 log CFU daily)	12 weeks	Daily	None specified	Placebo	Yes	None	Wilcoxon rank sum test
Mohammadi A.	2024	Probiotic supplement + 400 IU vitamin D per day	12 weeks	Once per day	None specified	Placebo	Yes	None	Not specified
Ohsawa K.	2018	Lactobacillus helveticus-fermented milk containing lactononadecapeptide (2.4 mg per bottle)	8 weeks	Once daily	None specified	Placebo	Yes	None	Student's t-test, Wilcoxon signed-rank test
Önning G.	2023	Lactiplantibacillus plantarum HEAL9 (LPHEAL9), 10B CFU per day	12 weeks	Once daily	None specified	Placebo	Yes	None	Mixed two-way ANOVA, Mann-Whitney U Test
Papalini S.	2018	Multispecies probiotic (Ecologic®Barrier)	28 days	Once daily, 2 g of powder	Not applicable	Placebo	Powder identical to the probiotic in appearance	Not applicable	Not mentioned
Roman P.	2019	*Streptococcus thermophilus*, *Bifidobacterium breve* (*B. breve*), *B. longum*, B. *infantis*, *Lactobacillus paracasei* (*L. paracasei*), *L. acidophilus. L. delbrueckii* subsp *bulgaricus*, and *L. plantarum*	12 weeks	Twice daily (every 12 h)	Not applicable	Placebo	Contained maltose and silicon dioxide as inactive agents	Not applicable	Frequency and percentage
Roman P.	2018	Multispecies probiotic (ERGYPHILUS Plus)	8 weeks	Twice daily (2 pills before breakfast and dinner)	Not applicable	Placebo	Inert pills identical in appearance to probiotics	Not applicable	Not explicitly mentioned
Rudzki L.	2018	Lactobacillus Plantarum 299v (LP299)	8 weeks	Twice daily (1 capsule in the morning and 1 at night)	Not applicable	Placebo	Capsules containing crystalline cellulose powder	Not applicable	Chi-square test
Ruiz-Gonzalez C.	2024	Multispecies probiotic containing Lactobacillus rhamnosus and Bifidobacterium lactis	10 weeks	Once daily	Not applicable	Placebo	Capsules containing potato starch	Not applicable	Not explicitly mentioned
Sakurai K.	2022	Heat-treated Lactiplantibacillus plantarum OLL2712	12 weeks	Once daily (1 g of powder)	Not applicable	Placebo	Dextrin powder without OLL2712	Not applicable	No reported harms or unintended effects
Sanborn V.	2020	Lactobacillus rhamnosus GG, 10 billion CFU	3 months	Two capsules daily	Not applicable	Placebo	Microcrystalline cellulose capsules identical in appearance to the probiotics	Not applicable	Chi-square test

Table 2 (continued)

First Author	Year	Intervention Content	Duration of Intervention	Frequency of Intervention	Co-Intervention Content	Control Type	Placebo	Control Active	Adverse Event Measure
Schneider E.	2023	Multistrain probiotic supplement containing 8 different strains	4 weeks	Once daily, 900 billion CFU/d	Not applicable	Placebo	Maltose powder without bacteria	Not applicable	No reported harms or unintended effects
Shi S.	2023	Probiotic Bifidobacterium longum BB68S (5×10^10 CFU/sachet)	8 weeks	Once daily after lunch or dinner	Not applicable	Placebo	Maltodextrin powder without probiotics	Not applicable	No significant differences in adverse effects between groups
Tamtaji O.	2019	Probiotic (L. acidophilus, B. bifidum, B. longum) and Selenium (200 mg/day)	12 weeks	Daily	Not applicable	Placebo	Starch capsules, identical in appearance to supplements	Selenium-only group	Not explicitly mentioned
Xiao J.	2020	Probiotic Bifidobacterium breve A1 (2×10^10 CFU)	16 weeks	Two capsules daily	Not applicable	Placebo	Maize starch capsules	Not applicable	No adverse events reported

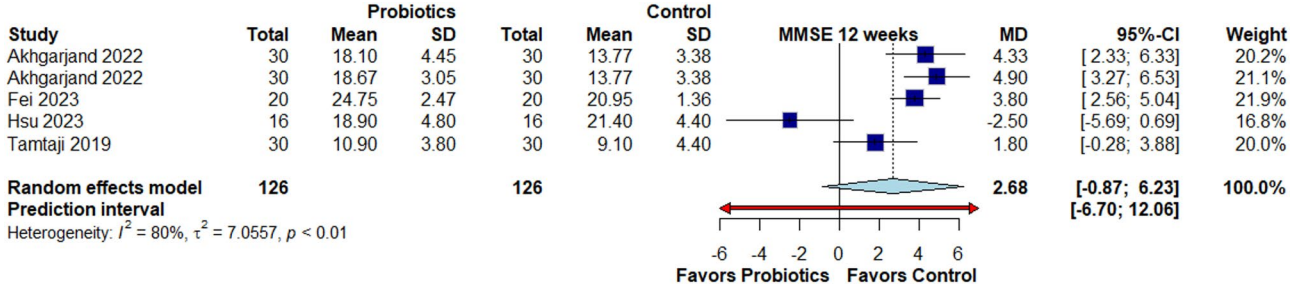

Fig. 2 Risk of bias assessment of included trials

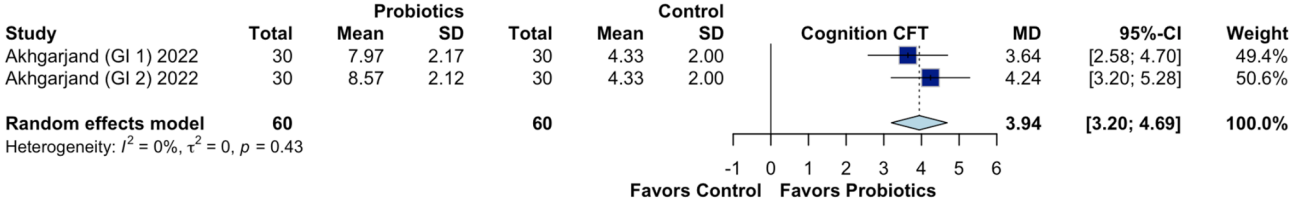

Fig. 3 MMSE at 8 weeks

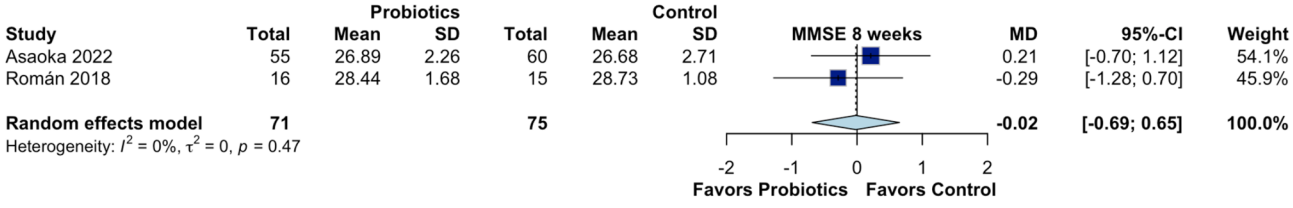

Fig. 4 MMSE at 12 weeks

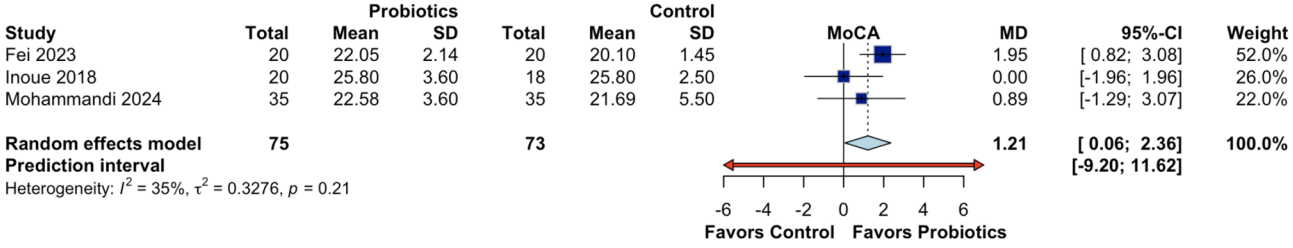

Fig. 5 MoCA test

1.13 to −8.22; moderate evidence), while in people with cognitive impairment including Three RCTS [36, 49, 54], the results were uncertain (MD: 2.38; 95% CI: −1.46 to 6.22; very low evidence). In healthy adults, including data from one RCT [26], no effect was observed (MD: 0.00; 95% CI: −1.96 to 1.96; high evidence) (Supplemental Fig. 1). Safety Outcomes.

The safety analysis included four RCTs [29, 34, 35, 52] with 325 participants. The relative risk of experiencing any adverse event was 0.91 (95% CI: 0.65 to 1.27), which translates to 24 fewer events per 1000 participants (95% CI: −93 to 72). The certainty of the evidence was very low (Fig. 7).

Sensitivity analysis

To assess the robustness of the findings, sensitivity analyses were conducted for MMSE at 8 and 12 weeks, as well as for MoCA at 12 weeks. The sensitivity analysis for MMSE at 8 weeks confirmed no significant cognitive improvement with probiotic supplementation, with a mean difference of −0.02 (95% CI: −0.69 to 0.65) and no observed heterogeneity (I^2 = 0.0%). For MMSE at 12 weeks, the association between probiotic supplementation and cognitive improvement persisted, with a mean difference of 4.23 (95% CI: −0.87 2.77 to 6.23), low heterogeneity was observed and no evidence of heterogeneity across studies (I^2 = 0.0%). For MoCA at 12 weeks, the sensitivity analysis supported a mean difference of 1.21 (95% CI: 0.06 to 2.36), with moderate heterogeneity (I^2 = 35.0%). These findings suggest that the primary results were robust, though the presence of moderate-to-high heterogeneity highlights the need for further research to explore potential sources of variability.

Heterogeneity metrics

Further analyses were conducted to evaluate the consistency of the findings. For MMSE at 8 weeks, there was no observed heterogeneity (I^2 = 0.0%, τ^2 = 0, p = 0.4655), suggesting methodological consistency across studies. For MMSE at 12 weeks, the effect remained statistically significant, with a mean difference of 4.23 (95% CI: 2.77 to 5.68), with no heterogeneity (I^2 = 80.0.0%, τ^2 = 0, p = 0.01). For MoCA at 12 weeks, the results remained stable across studies, with moderate heterogeneity (I^2 = 35.0%, τ^2 = 0.3276, p = 0.2145). These findings indicate that while probiotics may have a potential effect on cognitive function, the variability in study designs and probiotic interventions contributes to heterogeneity.

Discussion

In this systematic review and meta-analysis, we evaluated the efficacy and safety of probiotic supplementation on cognitive function. Our results demonstrated that probiotics significantly improved cognitive function after 12 weeks of treatment, although no notable improvement was observed at the 8-week mark. The primary outcomes showed that probiotics positively impacted cognitive performance as measured by the MMSE, MoCA and Cognition CFT assessments.

While our results indicate statistically significant improvements in MMSE (MD 4.23; 95% CI [2.77, 5.68]) MoCA (MD 1.21; 95% CI [0.06, 2.36]) and CFT (MD 3.94; 95% CI [3.20, 4.69]), it is critical to determine whether these changes translate into clinically meaningful cognitive benefits. Previous research suggests that a minimal clinically important difference (MCID) for the MoCA ranges between 1.0 and 2.0 points, particularly in populations at risk of cognitive decline [56]. Given our observed effect size, the improvement in MoCA scores likely holds clinical relevance, although the certainty of evidence remains low.

For CFT, prior studies indicate that an increase of approximately 3–5 words in verbal fluency tasks can reflect a meaningful improvement in cognitive function, particularly in aging populations and individuals with mild cognitive impairment (MCI) [57]. Our findings align with this threshold, suggesting potential clinical significance. However, the heterogeneity of the included studies, variations in baseline cognitive function, and differences in intervention duration necessitate further exploration in well-controlled trials.

The results of the MMSE, MoCA, and Cognition CFT at 12 weeks of follow-up have low certainty and limited clinical applicability due to high imprecision and risk of bias in the studies, especially due to the small sample size.

Our findings align with previous research that suggests a possible link between probiotics and cognitive improvements. The study by Mo et al. (2024), provided

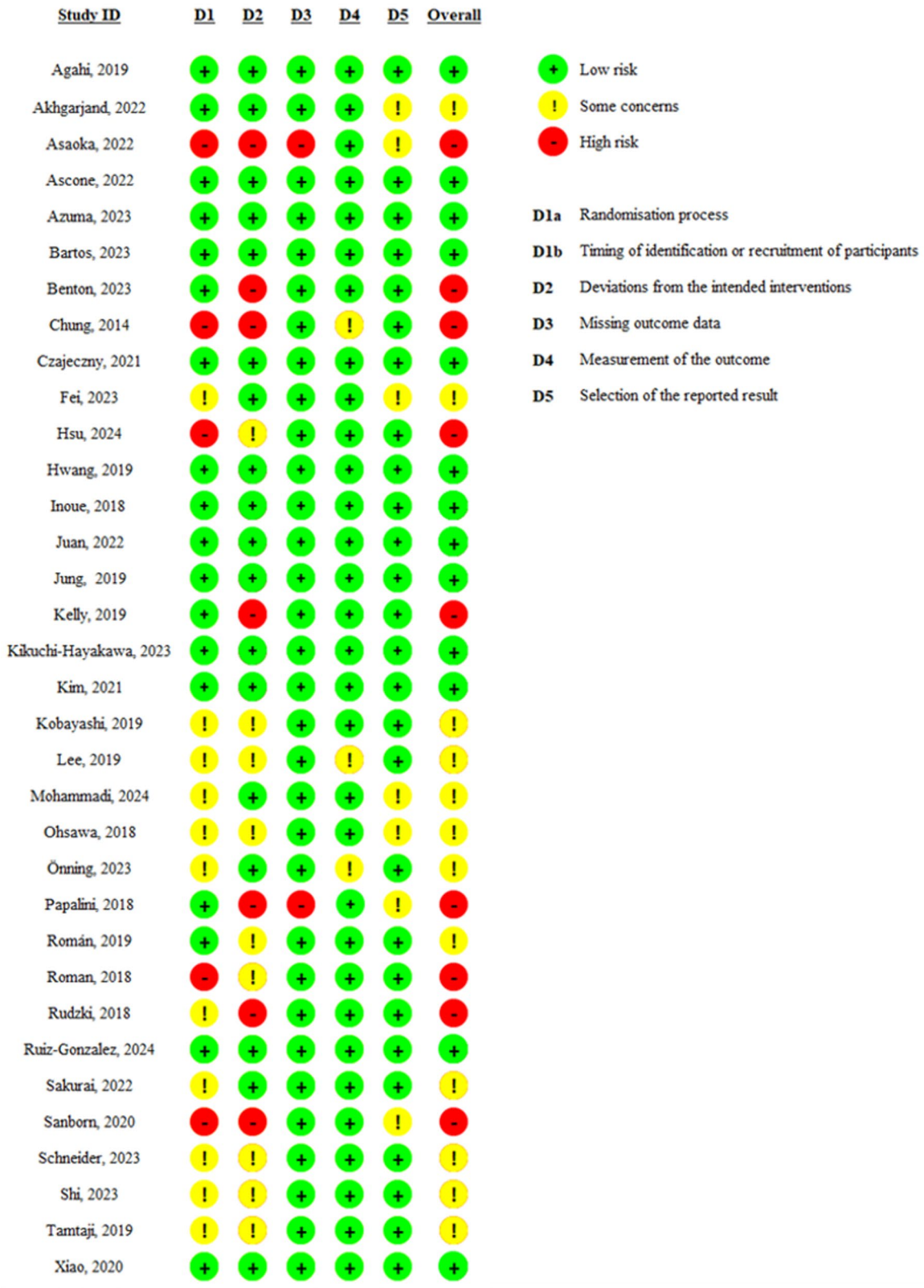

Fig. 6 Cognition CFT

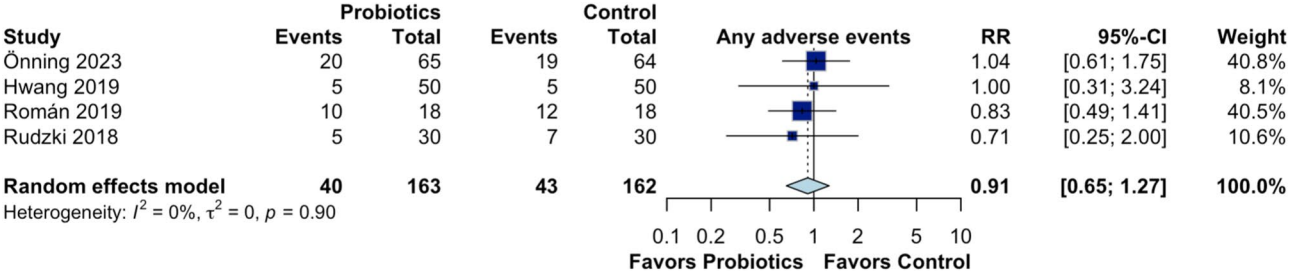

Fig. 7 Any adverse event

evidence that probiotics contributed to the improvement of global cognitive function (SMD = 0.67; 95% CI, 0.32, 1.02), recall/delayed memory (SMD = 0.67; 95% CI: 0.32, 1.02), attention (SMD = 0.31; 95% CI: 0.04, 0.58) and visuospatial/constructional (SMD = 0.24; 95% CI: 0.06, 0.42) cognitive domain in Alzheimer's disease and mild cognitive impairment [10]. Similarly, the study by Liu, Probiotic supplementation exerted a highly significant effect on cognitive function among individuals with cognitive impairment or Alzheimer's disease (SMD = 1.34; 95%CI, 0.51–2.16; $P < 0.01$). Conversely, in cognitively healthy individuals, probiotic supplementation appeared to have limited or no observable efficacy [5].

The methods in which probiotic supplementation influences cognitive function are explained by several routes. Studies have revealed a chronic neuroinflammatory state, marked by pro-inflammatory cytokine production, in AD patients [58]. This condition is thought to be connected to a persistent accumulation of Aβ in neurons. This neuroinflammation, which can impair neuronal activity, seems to be caused by dysbiosis, or an imbalance in the gut microbiota [59]. Consequently, adjuvant probiotic therapy may maximize the therapeutic benefits of AD medicines by preventing or maybe curing intestinal dysbiosis [60]. Probiotics influence cognitive performance in CFT through several mechanisms, such as modulation of the gut-brain axis, which influences cognitive performance through improved gut-brain communication; reduced inflammation, as memory and executive function, may be enhanced by the decreased brain and systemic inflammation; and production of neurotransmitters such as GABA and serotonin, which are related to language control and cognitive function. Finally, probiotics can improve mood and decrease anxiety, influencing the results of verbal fluency exercises [61]. The microbiome extends its influence to the brain through a variety of pathways linking the gut to the central nervous system. Probiotics, types of live microorganism that benefit the host, have been shown to alleviate gastrointestinal disease, boost immunity, and treat neurological disorders [62]. The Categorical Fluency Test is beneficial in identifying cognitive impairment and dementia, including Alzheimer's disease [42]. It is often used to assess executive functioning, semantic memory, and language skills.

Previous meta-analyses have examined the effects of probiotic supplementation on cognitive function, yet significant limitations persist in their methodologies and interpretations. Eastwood et al. (2021) reported that twenty-one out of thirty included studies reported improvements in at least one cognitive outcome measure, such as, long-term memory recall, spatial working memory, and language fluency, along with further enhancement in executive functioning and motor processing speed. Also, in aging adults, reported enhancement in delayed recall performance was measured by both the MMSE and the comprehensive cognitive assessment battery [63]. Widyadharma et al. (2024) reported a notable enhancement of cognition, including linguistic abilities, memory retention, spatial reasoning, and attentional as well as executive functioning with the probiotic group following the 12-week intervention [64].

The intestinal microbiota plays a crucial role in the development of Alzheimer's disease through various biological mechanisms, including the initiation of neuroinflammatory processes, irregularities in beta-amyloid processing, abnormal phosphorylation of tau proteins, imbalances in neurotransmitter activity, and heightened oxidative damage. Disruptions in the microbial ecosystem can lead to the dysfunction of these pathways and are linked to increased permeability of the blood-brain barrier, which facilitates inflammation in neural tissues and contributes to neuronal degeneration [65]. Baldi et al. (2021) highlighted potential benefits of probiotics on neuroinflammation and gut-brain axis modulation but acknowledged substantial heterogeneity due to variations in intervention duration, participant characteristics, and outcome measures [66].

A key controversy in this field revolves around the degree to which probiotic supplementation exerts clinically meaningful cognitive benefits. Some studies suggest improvements in cognitive performance [6, 67], while others report null or inconsistent findings [68] (Supplemental Table 5). This inconsistency may stem from variations in probiotic formulations, host microbiota

interactions, and differences in baseline cognitive function across study populations.

Although the results indicate that probiotics reduced adverse effects but did not achieve statistical significance, some patients in the groups receiving probiotics in the studies had notable harms such as vertigo, tremor, complications of cirrhosis (spontaneous bacterial peritonitis and grade 2 hepatic encephalopathy) or infections.

Another aspect to consider is that our study only included participants over 18 years of age because in this age group it is more common to develop cognitive impairment such as Alzheimer's disease [69]. In addition, no significant improvements were observed in healthy adults compared to impaired adults. This difference suggests that age, together with baseline cognitive status, could influence the response to probiotics, possibly due to changes in the microbiota and neuroinflammatory processes associated with aging [70]. These findings would indicate that caution should be taken in interpreting our results and that future studies with better methodological quality should take these limitations into account when making recommendations.

Despite the positive findings, several limitations should be acknowledged. First, the heterogeneity among the studies, particularly regarding the probiotic strains used, dosage regimens, and participant characteristics, may have introduced variability in the results. Additionally, some studies included in the review had concerns about randomization, blinding and number of the studies included, which could have impacted the internal validity and generalizability of the results. Although we conducted sensitivity analyses to account for these differences, the overall effect sizes should be interpreted cautiously.

Other limitation is the small number of studies included in the meta-analyses and the impossibility of performing population-based subgroup analyses. In addition, the certainty of the evidence, assessed using the GRADE tool, was rated as low in most of the included studies (3 outcomes had very low certainty and 2 had low certainty). This is mainly due to methodological heterogeneity among the randomized controlled trials (RCTs), including differences in the probiotic strains used, the doses administered, the duration of treatment, and the tools used to assess cognitive function.

A meta-analysis in adults under 50 years of age was also not possible due to insufficient statistical data and the heterogeneity of the outcome measures.

Our study addresses several of these strengths, offering a more comprehensive and methodologically rigorous synthesis of the evidence, following PISMA 2020 guidelines and ensuring transparency with the registered protocol in PROSPERO. We use cochrane RoB 2.0 and GRADE framework to evaluate certainty of evidence.

Another notable strength of our study is the inclusion of a sensitivity analysis using a common-effect model, allowing us to assess the robustness of our findings under different analytical assumptions. Unlike previous meta-analyses that did not adequately address strain heterogeneity, we attempted to standardize probiotic doses and categorize interventions based on strain-specific effects. Although a formal subgroup analysis could not be conducted due to the limited number of studies, our approach highlights the need for future trials to adopt more standardized probiotic interventions.

Furthermore, our study included a broader range of cognitive assessments, including MMSE, MoCA, and categorical fluency tests, providing a more comprehensive evaluation of cognitive function. We also considered both efficacy and safety outcomes, addressing concerns regarding the clinical utility and potential risks of probiotic supplementation.

The safety profile of probiotics remains an area of active investigation, particularly in vulnerable populations. Our analysis showed no significant reduction in adverse events with probiotic supplementation (RR 0.91; 95% CI [0.65, 1.27]; Certainty of evidence (CoE) was very low), suggesting that probiotics neither increase nor decrease overall risk. However, this finding must be interpreted with caution given the variability in adverse event reporting across studies.

Known risks of probiotic use include infections, particularly in immunocompromised individuals, those with severe comorbidities, or patients with central venous catheters. While the included trials did not specifically stratify adverse events by patient risk category, prior systematic reviews have noted rare but serious complications, such as bacteremia and fungemia in immunocompromised hosts. Future studies should incorporate stratified safety analyses to determine whether specific subgroups face increased risks.

Further research is necessary to confirm the long-term effects of probiotics on cognitive function, particularly in diverse populations and with larger sample sizes. Future trials should aim for standardized protocols, including consistent probiotic strains and dosages, to reduce heterogeneity and improve study comparability. In addition, adjustment of dose-response relationships may be necessary to mitigate this problem. Also, more extended follow-up periods will be critical to assess the sustainability of cognitive improvements and the potential for probiotics to prevent cognitive decline in the long term [71, 72].

Our findings are consistent with emerging evidence from recent clinical trials supporting the cognitive benefits of probiotic supplementation in older adults. For example, a double-blind randomized controlled trial by Rahmani et al. demonstrated significant improvements in global cognitive performance and verbal memory

following a 12-week probiotic intervention in elderly individuals with mild cognitive impairment. These results further underscore the potential of gut-brain axis modulation as a preventive or adjunctive strategy for cognitive decline in aging populations, although further large-scale and longer-term studies are warranted to confirm these effects and assess their durability over time [73].

In conclusion, our study provides evidence that probiotics can positively influence cognitive function, especially after 12 weeks of supplementation, using MoCA test. However, due to the very low certainty found in the majority of outcomes, the evidence is uncertain, so our results should be interpreted with caution. In addition, more rigorous studies (larger clinical trials, standardized cognitive assessments, studies with longer follow-ups) are needed to confirm these findings and establish probiotics as a viable intervention for cognitive impairment.

Abbreviations

MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
CFT	Categorical fluency test
RCT	Randomized controlled trial
CFU	Colony forming units
CoE	Certainty of evidence

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12906-025-05149-6.

Supplementary Material 1.

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All data generated or analyzed during this study are included in this published article and its supplementary information files.

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